See corresponding editorial on page 1390.

Maternal anemia and preterm birth among women living with HIV in the United States

Denise L Jacobson,[1] Daniela Neri,[2] Audrey Gaskins,[3] Lynn Yee,[4] Armando J Mendez,[5] Kristy Hendricks,[6] Suzanne Siminski,[7] Rebecca Zash,[8] Laurie Hyzy,[7] and Jennifer Jao,[9,10] for the Pediatric HIV/AIDS Cohort Study

[1]Center for Biostatistics in AIDS Research, Harvard TH Chan School of Public Health, Boston, MA, USA; [2]Center for Epidemiological Research in Nutrition and Health, University of São Paulo, São Paulo, Brazil; [3]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA; [4]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [5]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Leonard M Miller School of Medicine, University of Miami, Miami, FL, USA; [6]Dartmouth Medical School, Department of Pediatrics, Lebanon, NH, USA; [7]Frontier Science Technology Research Foundation INC, Amherst Office, NY, USA; [8]Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, MA, USA; [9]Division of Pediatric Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; and [10]Division of Adult Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

ABSTRACT

Background: Women living with HIV (WLHIV) have a higher prevalence of anemia than women without HIV, possibly related to the effects of HIV and antiretroviral medications.

Objectives: To estimate the prevalence of anemia in the third trimester of pregnancy and the effect of anemia on preterm births in WLHIV in the longitudinal, US-based Pediatric HIV/AIDS Cohort Study (PHACS).

Methods: During the third trimester, we obtained up to three 24-hour dietary recalls to estimate daily intakes of nutrients and measured serum concentrations of iron, vitamin B6, vitamin B12, zinc, folate, ferritin, total iron-binding capacity (TIBC), and high sensitivity C-reactive protein. Third trimester anemia was defined as hemoglobin < 11 g/d and iron-deficiency anemia (IDA) was defined as low ferritin, high TIBC, and low transferrin saturation. A preterm birth was defined as birth at < 37 completed weeks of gestation, regardless of etiology. We fit separate modified Poisson regression models for each outcome (anemia, preterm birth) and each main exposure, adjusted for confounders, and report adjusted prevalence ratios (aPR) and 95% CIs.

Results: Of the 267 WLHIV, 50% were anemic in the third trimester, of whom 43.5% (n = 57/131) had IDA. On average, women with anemia were younger, were more likely to be black, started antiretroviral medications in the second trimester, had a low CD4 count (<200 cells/mm^3) early in pregnancy, and were less likely to meet recommended intakes for iron, B6, and folate. The prevalence of anemia was greater in WLHIV with a low CD4 count (aPR = 1.65; 95% CI: 1.20–2.27) and high HIV viral load (>10,000 copies/mL; aPR = 1.38; 95% CI: 1.02–1.87). In total, 16% of women delivered preterm. Anemia was associated with a 2-fold (aPR = 2.04; 95% CI: 1.12–3.71) higher prevalence of preterm births.

Conclusions: Anemia is common in pregnant WLHIV, highlighting the need to address the underlying factors and clinical outcomes of anemia in this population. *Am J Clin Nutr* 2021;113:1402–1410.

Keywords: anemia, HIV infection, pregnancy, iron-deficiency, B vitamins, folate, dietary intake, preterm birth

Introduction

Anemia remains an important public health issue in women, due to its significant impacts on maternal morbidity and mortality and adverse birth outcomes (1). At least 42% (56 million) of pregnant women worldwide (2, 3) and 16.2% of pregnant women in the United States (4) are estimated to be anemic, with significant disparities by race and ethnicity. Anemia is 4–7 times more prevalent in women who identify as non-Hispanic black compared to those who identify as non-Hispanic white and is 2–3 times higher in Hispanic individuals compared to non-Hispanic white individuals (5). The WHO aims to reduce anemia by 50% in women of reproductive age, as 1 of 6 global nutrition targets for 2025 (6).

Women living with HIV (WLHIV) have a higher prevalence of anemia compared to women living without HIV, which may be due to the detrimental effects of HIV, including immunosuppression; an HIV viral burden; the use of specific antiretroviral medications (ARVs), such as zidovudine (ZDV); and poor diet, among other risk factors (7, 8). While improvements in the hemoglobin (Hgb) status are observed after initiation of combination antiretroviral therapy (cART) in men and women (7), anemia is a strong predictor of mortality after cART

initiation in low-to-middle income countries (9). The prevalence of anemia and its etiology are not well characterized among pregnant WLHIV in the cART era, including in the United States. The primary objectives of this analysis were to estimate the prevalence of anemia in the third trimester of pregnancy, characterize the proportion of pregnant women with anemia due to iron deficiency, and estimate the effects of anemia on preterm births in pregnant WLHIV enrolled in the US-based Pediatric HIV/AIDS Cohort Study (PHACS).

Methods

Participants

The Nutrition Substudy (R01HD060325) of the PHACS sequentially enrolled WLHIV between 19–39 weeks (median, 32 weeks) of gestation who were currently enrolled in the parent Surveillance Monitoring for Antiretroviral Therapy Toxicities Study (SMARTT) protocol of PHACS from 2009–2011 at 15 clinical sites (10, 11). The SMARTT protocol and the Nutrition Substudy were approved by the Institutional Review Board at each site, at the University of Miami Human Subjects Research Office, and at the Harvard TH Chan School of Public Health, and ethical procedures were followed. Informed consent was obtained from the mother for herself and on behalf of her child.

The Pediatric HIV/AIDS Cohort Study (PHACS) was supported by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development, with co-funding from the National Institute Of Dental & Craniofacial Research, the National Institute Of Allergy And Infectious Diseases, the National Institute Of Neurological Disorders And Stroke, the National Institute On Deafness And Other Communication Disorders, the National Institute Of Mental Health, the National Institute On Drug Abuse, the National Institute On Alcohol Abuse And Alcoholism, the National Cancer Institute, the Office of AIDS Research, and the National Heart, Lung, and Blood Institute through cooperative agreements with the Harvard TH Chan School of Public Health (HD052102; Principal Investigator, George R Seage III; Program Director, Liz Salomon) and the Tulane University School of Medicine (HD052104; Principal Investigator, Russell Van Dyke; Co-Principal Investigator, Ellen Chadwick; Project Director, Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (Principal Investigator, Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (Principal Investigator, Julie Davidson).

The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or US Department of Health and Human Services.

Supplemental Figures 1 and 2 and Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to DLJ (e-mail: jacobson@sdac.harvard.edu).

Abbreviations used: aPR, adjusted prevalence ratios; ART, antiretroviral therapy; ARV, antiretroviral medication; cART, combination antiretroviral therapy; Hgb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; IDA, iron-deficiency anemia; NDSR, Nutrition Data System for Research; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PHACS, Pediatric HIV/AIDS Cohort Study; PI, protease inhibitor; SGA, small for gestational age; SMARTT, Surveillance Monitoring for Antiretroviral Therapy Toxicities; TIBC, total iron-binding capacity; WLHIV, women living with HIV; ZDV, zidovudine.

Received August 5, 2020. Accepted for publication December 21, 2020.

First published online March 10, 2021; doi: https://doi.org/10.1093/ajcn/nqaa441.

To be included in this analysis, women enrolled in the Nutrition Substudy were required to have at least 1 Hgb value from the third trimester of pregnancy, have at least 1 valid dietary recall, have delivered a liveborn infant with a known gestational age at birth, and have a recorded birth weight for the infant. Women were excluded from the analysis if they delivered twins or higher order gestation, if they had a history of gastric bypass surgery, or if all their dietary recalls did not reflect usual intakes (i.e., were conducted during hospitalization).

Data collection

Sociodemographics, clinical history, and body measurements.

Women self-reported their socio-demographic status and substance use, based on the Substance Use Inventory used in the Maternal Lifestyles Study (11, 12), during the current pregnancy. Race is collected in the following categories: American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander, black or African American, white, and not reported. Hispanic ethnicity is also self-reported.

Clinical history about the current pregnancy was abstracted from the medical chart, including pre-pregnancy weight (kg) and height (cm), pregnancy and birth complications, hepatitis B or C coinfection, CD4 count and HIV viral load (RNA) in pregnancy, gestational age of prenatal care initiation, year of HIV diagnosis, and ARVs used during the pregnancy. When possible, gestational dating was confirmed by an ultrasound at each site, per the usual clinical practice, and the dating criteria were abstracted. The pre-pregnancy BMI was calculated as weight divided by height squared (kg/m^2). Women were classified as having hepatitis B if both surface antigen and core antibody tests were positive and were classified as having hepatitis C if a hepatitis C RNA test was positive.

Anemia.

All available Hgb measures in the third trimester (28 weeks of gestation or greater) were abstracted from the obstetric records. The average of those measures was calculated for each woman, and anemia was defined as an average Hgb < 11 g/dL, based on the WHO criteria for pregnancy (13). Moderate/severe anemia was defined as an Hgb < 10 g/dL.

To further understand the prevalence of iron-deficiency anemia (IDA) and describe other potential nutritional and dietary factors associated with anemia, nonfasting blood was drawn in the third trimester of pregnancy. The samples were not drawn at the same time of day. The serum was stored at $-70°C$ until samples were sent to the Laboratory of Armando Mendez at the University of Miami Diabetes Research Institute to be assayed for concentrations of anemia-associated factors. These included iron, vitamin B6, vitamin B12, zinc, folate, ferritin, total iron-binding capacity (TIBC), and high-sensitivity C-reactive protein (hsCRP). Vitamin B6 (pyridoxal 5'-phosphate) was measured utilizing a specific enzymatic assay (Buhlmann Diagnostics Corp), following the manufacturer's protocol. All other analytes were measured on a Cobas 6000 autoanalyzer (Roche Diagnostics), using the manufacturer's reagents and following all instructions for instrument set up, assay calibration, and sample measurement. In the presence of chronic inflammation, such as in those living with HIV, ferritin may be elevated due to its role as an acute phase reactant and may not adequately reflect iron stores. Thus, low

ferritin was defined as <12 μg/L when hsCRP was ≤10 mg/L and as <30 μg/L when hsCRP concentrations were greater than 10 mg/L (14–16). High TIBC concentrations were defined as >450 μg/dL, based on the standard clinical definition. Transferrin saturation (%) was calculated as [serum iron (μg/dL)/TIBC (μg/dL)] * 100%, with concentrations <16% considered low (17). We created 2 additional variables with higher cutoffs to define low ferritin as <45 μg/L (18, 19) and low transferrin saturation as <20%. Abnormal concentrations of the following laboratory assessments in pregnancy were based on published studies: iron < 30 μg/dL; B6 < 20 nmol/L; B12 < 400 pg/mL; folate < 4.5 ng/mL; zinc < 50 μmol/L; and hsCRP > 10.0 mg/L (15). We classified IDA as low ferritin, high TIBC, and low transferrin saturation.

Nutritional intake and food security.

Women were interviewed in a standardized fashion, using study-provided cell phones, by a trained nutritionist at the University of Miami (DN and another staff nutritionist) to obtain three 24-hour dietary recalls (from 2 weekdays and 1 weekend day, over a 2-week period) during the third trimester of pregnancy (Week 28 to delivery) (20). The 24-hour dietary recalls were obtained following the multiple pass method (21). Dietary intake and micronutrient supplement data were analyzed using the Nutrition Data System for Research (NDSR), versions 2010 and 2011 (Nutrition Coordinating Center, NDSR Software, http://www.ncc.umn.edu/products/). Micronutrient supplement data related to the past 30 days were collected at the end of the first 24-hour recall interview using the Dietary Supplement Assessment Module included in the NDSR. Macro- and micronutrient intakes were generated for each 24-hour recall separately, as well as for supplement use. A protocol for quality assurance suggested by the NDSR was carried out by a team of 3 nutritionists, and outlying values for energy, macronutrients, and key micronutrients were checked for validity. Data deemed invalid/unreliable were excluded.

Dietary intake data were assessed using means of all recall days, when available, or data from 1 day otherwise. Using the RDAs for pregnant women, we classified intakes [diet alone, diet plus supplements (total)] as below the RDA, within the RDA, or above the RDA (15). For this analysis, we include iron, pyridoxine (B6), cobalamin (B12), and folate (22). The US Household Food Security Survey Module: 6-Item Short Form was administered during the first dietary phone interview to evaluate food security over the last 12 months. Food security was categorized as high/moderate, low, or very low (23).

Preterm birth and infant anthropometrics.

A preterm birth was defined as a gestational age < 37 weeks at birth (24). Gestational age was abstracted from the medical chart and determined by standardized obstetric procedures, including dating based on first trimester ultrasound measurement confirmation, clinical findings, or a combination of the 2, or based on the last menstrual period. Birth weight (g) was abstracted from the clinical chart. Using standard techniques, we measured length within 14 days of birth (herein called birth length). Z-scores for sex and gestational age were calculated for birth weight, length, and BMI based on reference values (25). Being small for gestational age (SGA) was defined as having a weight < 10th percentile for gestational age.

Statistical analysis

The distributions of socioeconomic and clinical factors, serologic assays, and nutrient intakes were described by the median (IQR) and number (%) and compared by anemia status using a Fisher's exact test for categorical variables and a Student's *t*-test for continuous variables.

We fit separate, modified Poisson regression models (26) for each outcome and each main exposure of interest to obtain a prevalence ratio and 95% CI for each unadjusted and adjusted prevalence ratio model. First, models were fit to examine the prevalence of anemia by each of the following exposures separately: *1*) earliest CD4 count in the first or second trimester [<200 cells/mm^3, 201–499 cells/mm^3, ≥500 cells/mm^3 (reference)]; *2*) earliest HIV viral load in the first or second trimester [≤400 copies/mL (reference), 401–1000 copies/mL, 1001–10,000 copies/mL, >10,000 copies/mL]; and *3*) ARV class at last menstrual period or at earliest initiation of ARV in the first or second trimester [protease inhibitor (PI) without a non-nucleoside reverse transcriptase inhibitor (NNRTI; reference), NNRTI with/without a PI, nucleoside reverse transcriptase inhibitor (NRTI) without a PI or NNRTI, other, or no initiation before second trimester]. Second, models were fit to examine the prevalence of preterm births by third trimester anemia. Potential confounders, in adjusted models, were selected a priori based on the literature and construction of directed acyclic graphs (27). Adjusted models for the anemia outcome included maternal age (years), race (black vs. non-black), income (<$10,000 vs. ≥$10,000/y), any alcohol use in pregnancy, and ZDV use at the last menstrual period or at the earliest initiation of ARV in the first or second trimester. Hispanic ethnicity was not deemed to be a confounder, and thus was not adjusted for in models. The adjusted model of preterm birth outcomes included maternal age, race, income, any alcohol use in pregnancy, PI use at last menstrual period or at earliest initiation of ARV in the first or second trimester in pregnancy, and pre-pregnancy BMI (<25, 25–29.9, 30–34.9, ≥35), as defined above. All analyses were performed in SAS 9.4 (SAS Institute).

Results

Included participants

Of the 317 pregnant women initially considered eligible who consented to participate in the Nutrition Substudy, we excluded 20 women with no valid dietary recall, 18 missing third trimester Hgb results, 3 with twin gestations, 1 with bariatric surgery, 2 with incorrect gestational ages, 4 missing birth weights, and 2 with implausible z-scores for birth anthropometrics (**Supplemental Figure 1**). This analysis therefore includes 267 women, of whom 220 (82%), 29 (11%), and 18 (7%), completed 3, 2, and 1 valid 24-hour dietary recalls, respectively.

Maternal characteristics

Maternal characteristics are shown in **Table 1**. Briefly, across all included women, the median maternal age was 28.4 years;

TABLE 1 Maternal characteristics by third trimester anemia among women living with HIV

Characteristic		Anemia, Hgb < 11 g/dL, Trimester 3			
		Yes,[1] $n = 134$	No,[1] $n = 133$	Total, $n = 267$	P value[2]
Average hemoglobin, g/dL, Trimester 3	Median (Q1, Q3)	10.1 (9.5, 10.5)	11.8 (11.5, 12.4)	11.0 (10.1, 11.8)	<0.001
Maternal age at delivery, y	Median (Q1, Q3)	27.8 (23.0, 31.6)	29.5 (23.6, 34.1)	28.4 (23.3, 33.3)	0.094
Black/non-black	Black	99 (76%)	73 (57%)	172 (67%)	0.002
	Non-black	31 (24%)	54 (42%)	85 (33%)	
Hispanic	Yes	36 (27%)	58 (44%)	94 (35%)	0.005
High school education	<high school	43 (32%)	42 (32%)	85 (32%)	1.00
	≥high school	91 (68%)	88 (68%)	179 (68%)	
Household income, US$	≥$10K/y	46 (38%)	53 (45%)	99 (41%)	0.29
	<$10K/y	76 (62%)	65 (55%)	141 (59%)	
Marital status	Living with partner/spouse	64 (48%)	69 (53%)	133 (50%)	0.39
	Single	70 (52%)	61 (47%)	131 (50%)	
Illicit drugs ever used in pregnancy	Yes	14 (11%)	12 (9%)	26 (10%)	0.84
Alcohol ever used in pregnancy	Yes	11 (8%)	16 (12%)	27 (10%)	0.32
Tobacco ever used in pregnancy	Yes	27 (20%)	23 (17%)	50 (19%)	0.64
Maternal pre-pregnancy BMI, kg/m^2	≥35.0	18 (16%)	27 (25%)	45 (20%)	0.38
	30.0–34.9	21 (19%)	20 (19%)	41 (19%)	
	25.0–29.9	30 (27%)	28 (26%)	58 (26%)	
	<25	43 (38%)	33 (31%)	76 (35%)	
Trimester started prenatal care	First trimester	85 (64%)	95 (73%)	180 (69%)	0.40
	Second trimester	40 (30%)	32 (25%)	72 (27%)	
	Third trimester	4 (3%)	2 (2%)	6 (2%)	
	Within 3 days of delivery	3 (2%)	1 (1%)	4 (2%)	
HIV diagnosis before this pregnancy	Yes	105 (80%)	105 (80%)	210 (80%)	1.00
ARV use before this pregnancy	Yes	91 (68%)	88 (66%)	179 (67%)	0.80
Timing of ARV initiation in pregnancy	Third trimester	6 (5%)	7 (5%)	13 (5%)	0.009
	Second trimester	62 (47%)	38 (29%)	100 (38%)	
	First trimester	19 (14%)	36 (27%)	55 (21%)	
	On at LMP	45 (34%)	51 (39%)	96 (36%)	
ART class at LMP or first/second trimester	Not on ART	8 (6%)	8 (6%)	16 (6%)	0.74
	Other	7 (5%)	8 (6%)	15 (6%)	
	NRTI, no PI or NNRTI	7 (5%)	3 (2%)	10 (4%)	
	NNRTI, w/ or w/o PI	10 (7%)	13 (10%)	23 (9%)	
	PI yes, NNRTI no	102 (76%)	101 (76%)	203 (76%)	
ZDV use in first/second trimester at first ARV use	Yes	56 (44%)	52 (42%)	108 (43%)	0.70
Earliest CD4 in the first/second trimester, cells/mm^3	<200	20 (16%)	8 (6%)	28 (11%)	0.020
	200–499	52 (42%)	49 (39%)	101 (40%)	
	≥500	52 (42%)	70 (55%)	122 (49%)	
Earliest HIV RNA in the first or second trimester, copies/mL	>10,000	37 (29%)	25 (20%)	62 (25%)	0.12
	1001–10,000	32 (25%)	30 (25%)	62 (25%)	
	400–1000	12 (10%)	7 (6%)	19 (8%)	
	<400	45 (36%)	60 (49%)	105 (42%)	

Abbreviations: ART, antiretroviral therapy; ARV, antiretrovirals; Hgb, hemoglobin; LMP, last menstrual period; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; ZDV, zidovudine.

[1]The number of missing values in anemic and nonanemic women, respectively, for the following variables: black/non-black (4, 6); high school education (0, 3); income (12, 15); marital status (0, 3); illicit drug use/alcohol use/tobacco use in pregnancy (1, 1); pre-pregnancy BMI (22, 25); trimester started prenatal care (2, 3); HIV diagnosis before this pregnancy (3, 1); timing of ARV initiation (2, 1); ZDV use in first/second trimester at first ARV use (8, 8); earliest CD4 in the first/second trimester (10, 6); and earliest HIV RNA in the first/second trimester (8, 11).

[2]P values were computed using a t-test for continuous variables and a Fisher's exact test for categorical variables.

67% identified as black and 35% as Hispanic. A third of women did not complete high school, approximately half had a household income <$10,000 per year, and half were single. Ever having used illicit drugs, alcohol, or tobacco during pregnancy was reported among 10%, 10%, and 19% of women, respectively. Most women reported prenatal care initiation in the first trimester, diagnosis of HIV infection before this pregnancy, and some ARV use prior to this pregnancy. Half received antiretroviral therapy (ART) at their last menstrual period or started in the first trimester, while 38% began in the second trimester. The majority of women who started ART during or before the second trimester were on a PI without a NNRTI (76%). The early CD4 count was <200 cells/mm^3 in 11% of women and the early viral load was >10,000 copies/mL in 25% of women.

TABLE 2 Maternal anemia–associated laboratory measures by third trimester anemia among women living with HIV

Characteristic		Anemia, Hgb < 11 g/dL, Trimester 3		
		Yes,[1] $n = 134$	No,[1] $n = 133$	P value[2]
Iron, μg/dL	Median (Q1, Q3)	47.0 (31.5, 72.5)	69.0 (55.0, 96.0)	<0.001
Iron < 30 μg/dL	Yes	25 (19%)	1 (1%)	<0.001
Ferritin, ng/mL	Median (Q1, Q3)	11.5 (7.8, 20.3)	18.8 (12.6, 27.9)	0.001
hsCRP > 10.0 mg/L	Yes	27 (20%)	28 (21%)	1.00
Low ferritin, after correction for inflammation	Yes	83 (63%)	47 (36%)	<0.001
Low ferritin < 45 ng/mL, not corrected for inflammation	Yes	123 (93%)	118 (89%)	0.38
Total iron-binding capacity, μg/dL	Median (Q1, Q3)	442 (366, 520)	370 (323, 429)	<0.001
Total iron-binding capacity > 450 μg/dL	Yes	65 (50%)	25 (19%)	<0.001
Transferrin saturation, %	Median (Q1, Q3)	9.9 (6.3, 19.8)	19.0 (14.1, 27.6)	<0.001
Low serum transferrin saturation < 16%	Yes	86 (66%)	46 (35%)	<0.001
Low serum transferrin saturation < 20%	Yes	100 (76%)	73 (56%)	<0.001
Vitamin B6, nmol/L	Median (Q1, Q3)	14.0 (8.7, 23.2)	20.6 (11.5, 39.0)	0.16
Vitamin B6 < 20 nmol/L	Yes	90 (68%)	65 (49%)	0.003
Vitamin B12, pg/mL	Median (Q1, Q3)	291.2 (232.4, 412.8)	367.20 (286.75, 500.90)	0.62
Vitamin B12 < 400 pg/mL	Yes	97 (73%)	71 (54%)	0.001
Folate, ng/mL	Median (Q1, Q3)	13.1 (9.0, 18.8)	16.9 (11.2, 23.5)	<0.001
Folate < 4.5 ng/mL	Yes	6 (5%)	0 (0%)	0.029
Zinc, μg/L	Median (Q1, Q3)	9.9 (7.7, 15.8)	10.3 (7.9, 17.9)	0.19
Zinc < 50 μmol/L	Yes	131 (100%)	132 (100%)	
Low serum B12 (<400 pg/mL) or low folate (<4.5 ng/mL)	Yes	99 (75%)	71 (54%)	<0.001

Abbreviations: Hgb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; TIBC, total iron-binding capacity.

[1]Missing among anemic and non-anemic women, respectively, for the following variables: iron (2, 2); hsCRP (2, 1); TIBC (3, 3); transferrin saturation (3, 3); B6 (2, 1); B12 (2, 1); folate (2, 1); and zinc (3, 1).

[2]P values were computed using a t-test for continuous variables and a Fisher's exact test for categorical variables.

Maternal characteristics by anemia status in the third trimester

Maternal characteristics were compared by anemia status. The median Hgb concentration in the third trimester was 11 g/dL overall; 50% (134/267) had anemia (Table 1) and 20% (54/267) had moderate/severe anemia. Compared to women without anemia in the third trimester, there was a trend for women with anemia to be younger, be black, be non-Hispanic, have started ART in the second trimester, and have a CD4 count < 200 cells/mm^3 early in pregnancy. No differences in education, income, marital status, substance use in pregnancy, the trimester in which they started prenatal care, ART class use, early ZDV use in pregnancy, early HIV viral load in pregnancy, or rates of viral hepatitis infection (not shown) were seen between groups (25).

Etiology of anemia in the third trimester.

Women with any anemia in the third trimester had a greater frequency of low serum iron (19% vs. 1%, respectively), ferritin after correction for inflammation (63% vs. 36%, respectively), and transferrin saturation (66% vs. 35%, respectively) or high TIBC (50% vs. 19%, respectively) compared to nonanemic women (**Table 2**). Of the 131 women with anemia who had data on ferritin, TIBC, and transferrin saturation, 43.5% ($n = 57$) were classified as having IDA (low ferritin, high TIBC, and low transferrin saturation) in the third trimester, while 74.0% had at least 1 of these criteria. In additional analyses, women with any anemia in the third trimester had a greater frequency of ferritin < 45 ng/mL, not corrected for inflammation (93% vs. 89%, respectively), and transferrin saturation < 20% (76% vs. 56%, respectively) compared to nonanemic women. Using these cutoffs and high TIBC, 48.1% ($n = 63$) of women with anemia were classified as having IDA, while 96.2% had at least 1 of these criteria. Among nonanemic women, 9.9% had iron deficiency based on the initial criteria, while 16.8% had iron deficiency using the more relaxed thresholds.

Among 262 women with information about food security, 25% had low food security and 12% had very low food security, with similar proportions by anemia status (**Table 3**). Women with anemia had slightly lower use of supplements—although use was very good in both groups—and were more likely to have intakes below the RDAs from diet and supplements for iron, B6, and folate. Few women in either group consumed less than the RDA for B12.

When anemia was defined as Hgb < 10 g/d versus ≥10 g/dL, we observed similar results (**Supplemental Tables 1** and **2**) as those reported above for Hgb < 11 g/dL.

Models of HIV-associated factors with anemia

The adjusted prevalence of anemia in the third trimester was 1.65 (95% CI: 1.20–2.27) times higher in women with a CD4 count < 200 cells/mm^3 compared to >500 cells/mm^3 (**Table 4**), based on a modified Poisson regression analysis. Women with an HIV viral load > 10,000 copies/mL had a 1.38 (95% CI: 1.02–1.87) times higher adjusted prevalence of anemia compared to those with a viral load < 400 copies/mL. In contrast, there was no strong association of PI use with anemia in this cohort of pregnant WLHIV.

TABLE 3 Maternal intake of micronutrients by third trimester anemia among women living with HIV

Characteristic		Anemia, Hgb < 11 g/dL, Trimester 3		
		Yes,[1] $n = 134$	No,[1] $n = 133$	P value[2]
Food security	High/marginal	85 (65%)	81 (62%)	0.84
	Low	32 (24%)	33 (25%)	
	Very low	14 (11%)	17 (13%)	
Used any supplements	Yes	124 (93%)	130 (98%)	0.084
Iron, mg/d, intake from supplements	Median (Q1, Q3)	28.0 (27.0, 91.1)	28.0 (27.0, 85.5)	0.70
Iron, mg/d, intake from diet and supplements	Median (Q1, Q3)	46.5 (36.2, 101.0)	43.7 (37.5, 95.9)	0.91
Iron, mg/d, RDA, diet and supplements	Below RDA	23 (17%)	8 (6%)	0.001
	Met RDA	41 (31%)	65 (49%)	
	Above RDA	70 (52%)	60 (45%)	
Vitamin B6, mg/d, daily intake from diet and supplements	Median (Q1, Q3)	4.2 (3.3, 5.0)	4.2 (3.7, 5.0)	0.33
Vitamin B6, mg/d, RDA, diet and supplements	Below RDA	15 (11%)	4 (3%)	0.015
	Met RDA	119 (89%)	129 (97%)	
Vitamin B12, μg/d, intake from supplements	Median (Q1, Q3)	7.5 (4.0, 8.0)	8.0 (4.0, 8.0)	0.45
Vitamin B12, μg/d, intake from diet and supplements	Median (Q1, Q3)	10.8 (7.0, 13.8)	11.1 (9.3, 13.9)	0.41
Vitamin B12, μg/d, RDA, diet and supplements	Below RDA	7 (5%)	2 (2%)	0.17
	Met RDA	127 (95%)	131 (98%)	
Folate, μg/d, intake from supplements	Median (Q1, Q3)	800 (400, 800)	800 (800, 800)	<0.001
Folate, μg/d, intake from diet and supplements	Median (Q1, Q3)	1143 (914, 1355)	1169 (1056, 1383)	0.024
Folate, μg/d, RDA, diet and supplements	Below RDA	25 (19%)	6 (5%)	<0.001
	Met RDA	17 (13%)	13 (10%)	
	Above RDA	92 (69%)	114 (86%)	

Abbreviation: Hgb, hemoglobin.

[1]Missing among anemic and non-anemic, respectively, for food security (3, 2).

[2]P values were computed using a t-test for continuous variables and a Fisher's exact test for categorical variables.

Birth characteristics

The median gestational age at delivery was 38.3 wk. The median birth weight, length, and BMI z-scores were −0.21 (IQR, −1.87 to 3.75), −0.10 (IQR, −3.03 to 3.57), and −0.24 (IQR, −2.69 to 3.25), respectively. Infants born to anemic women compared to nonanemic women tended to have lower median z-score values for gestational age for birth weight [−0.32 (25th, −1.8; 75th, 3.0) vs. −0.16 (25th, −1.8; 75th, 3.7), respectively; $P = 0.09$] and birth length [−0.18 (25th, −3.0; 75th, 2.2) vs. −0.10 (25th, −1.85; 75th, 3.6), respectively; $P = 0.061$].

TABLE 4 Models of third trimester anemia and preterm birth outcomes in pregnant women living with HIV

Model			Unadjusted		Adjusted[1,2]	
Outcome	Exposure of interest	Category level of exposure	Prevalence ratio (95% CI)	P value	Prevalence ratio (95% CI)	P value
Anemia, Hgb < 11 g/dL	Earliest ARV class in Trimester 1 or 2	Not on ART	1.00 (0.60–1.66)	0.985	0.82 (0.48–1.42)	0.48
		Other	0.93 (0.53–1.62)	0.795	0.86 (0.49–1.52)	0.61
		NRTI, no PI or NNRTI	1.39 (0.91–2.14)	0.129	1.23 (0.81–1.86)	0.34
		NNRTI, w or w/o PI	0.87 (0.53–1.41)	0.559	0.84 (0.50–1.40)	0.50
		PI yes, NNRTI no	—		—	
	Earliest CD4 count in Trimester 1 or 2, cells/mm^3	<200	1.68 (1.23–2.29)	0.001	1.65 (1.20–2.27)	0.002
		200–499	1.21 (0.91–1.60)	0.186	1.26 (0.96–1.66)	0.095
		≥500	—		—	
	Earliest viral load in Trimester 1 or 2 (copies/mL)	>10,000	1.39 (1.03–1.88)	0.031	1.38 (1.02–1.87)	0.038
		1001–10,000	1.20 (0.87–1.67)	0.265	1.12 (0.81–1.55)	0.50
		400–1000	1.47 (0.98–2.22)	0.063	1.36 (0.92–2.00)	0.12
		<400	—		—	
Preterm birth	Anemia	Hgb < 11 vs. ≥11 g/dL	1.99 (1.09–3.60)	0.024	2.04 (1.12–3.71)	0.019

Abbreviations: ART, antiretroviral therapy; ARV, antiretrovirals; Hgb, hemoglobin; LMP, last menstrual period; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

[1]Models for anemia outcomes were fitted with a modified Poisson regression analysis adjusted for maternal age (y), black race vs. non-black, income (<$10K/y, ≥$10K/y, missing), alcohol use (yes/no), and zidovudine at first ARV use at LMP or initiated ARV in the first/second trimester (yes/no).

[2]The model for preterm birth outcomes was fitted with a modified Poisson regression analysis adjusted for maternal age (y), black race vs. non-black, income (<$10K/y, ≥$10K/y, missing), alcohol use (yes/no), protease inhibitor use at first ARV use at LMP or initiated ARV in the first/second trimester (yes/no), and BMI (<25.0, 25.0–29.9, 30.0–34.9, ≥35).

Association of anemia with preterm birth

In total, 16% of infants in the Nutrition Substudy were born preterm; 9% were SGA and 11% weighed <2500 g at birth. The prevalence of preterm births was 11% (14/133) among women with Hgb ≥ 11 g/dL, 20% (16/80) in those with Hgb 10.0–10.9 g/dL, and 22% (12/54) in those with Hgb < 10 g/dL. Because the preterm birth prevalence was similar in the latter 2 groups, they were combined for the analysis of preterm births. Women with anemia (Hgb < 11 g/dL) in the third trimester had a 2-fold higher prevalence of preterm births than those without anemia (adjusted RR = 2.04; 95% CI: 1.12–3.71; Table 4), based on a modified Poisson regression analysis.

Discussion

Anemia is of particular concern during pregnancy, especially in vulnerable populations such as WLHIV, for whom there is an elevated risk of poor outcomes, including preterm births (1, 24). Half of the women in our cohort were anemic in the third trimester of pregnancy, with 20% exhibiting moderate/severe anemia. Both immunosuppression and a high HIV viral burden early in pregnancy were associated with third trimester anemia, as was the underlying iron nutritional status. Of the anemic women, 43% met the criteria for having IDA. Compared to nonanemic women, a higher percentage of anemic women failed to meet the daily RDAs from diet and supplements for iron, B6, and folate and had lower serum concentrations of these nutrients, as well as B12. WLHIV with third trimester anemia had a 2-fold greater risk of a preterm birth, highlighting the need to address the clinical outcomes of anemia in pregnancy in this population.

The 50% prevalence of anemia (13) in our cohort of pregnant WLHIV is similar to the 50% prevalence reported in Italian pregnant WLHIV (28), but lower than the 64% prevalence reported among pregnant WLHIV in low- and middle-income countries (29). However, compared to the 8.8% prevalence of anemia in the general US population of pregnant women, our prevalence is much higher (5). While anemia rates decline after the introduction of cART, it is still a common hematologic abnormality in WLHIV (28–30). In a study of nonpregnant US-based WLHIV, women with anemia had greater HIV disease severity, had less time on cART, and a greater proportion received ZDV (30). This suggests that the HIV disease severity may be a key factor driving anemia.

Proposed mechanisms include a direct effect of HIV on hematopoietic progenitor cells and activation of inflammatory pathways by HIV proteins, resulting in abnormal cytokine concentrations in the bone marrow environment. IL-6 stimulates the expression of hepcidin, a central regulator of iron homeostasis. Hepcidin facilitates the sequestration of iron within reticuloendothelial cells, which in turn limits iron availability for immature erythroid cells. In addition, leptin may impair erythropoietin responsiveness by promoting hepcidin production (31). These mechanisms are similar to those in aging populations, referred to as "anemia of inflammation" (32), and may be relevant to our cohort. While general systemic inflammation, as measured by hsCRP, did not differ in women with or without anemia in our cohort, CD4 counts were lower and viral burdens were higher in women with anemia.

Micronutrient deficiencies are an additional driver of anemia in the general population and should be considered in the context of HIV. Of the anemic women in our cohort, 43% were classified as having IDA. Although this is lower than the 42% prevalence reported in a study by Auerbach et al. (33) in a general population of pregnant women, had we used the same criteria as that study (ferritin < 30 ng/mL without correction for inflammation or transferrin saturation < 20%), our prevalence would have been 78.6%. Despite a similar percentage of low food security, women with anemia were less likely to meet the daily total intakes from diet and supplements for iron, B6, and folate, and had lower serum concentrations of these nutrients, as well as B12. Other studies have found inadequate nutrient intakes in persons living with HIV (34, 35). In addition to inadequate intakes of micronutrients, poor gut integrity could modify the metabolism of micronutrients and the absorption due to microbial dysbiosis, as commonly observed in persons living with HIV (36). Finally, black women in our study were more likely to be anemic, a finding that mirrors that data from pregnant women living without HIV in NHANES (37) and that could be related to socioeconomic differences, access to care, or stress.

In our cohort, pregnant WLHIV with anemia had a 2-fold greater risk of delivering preterm. A meta-analysis of randomized trials of daily iron supplementation with or without folate during pregnancy in women living without HIV shows increases in Hgb during pregnancy, but neither iron supplementation nor higher Hgb concentrations had an effect on preterm birth (1). A meta-analysis of observational studies shows a 1.28 greater risk of preterm births in pregnant women with anemia, irrespective of time of the anemia assessment (1). In a cohort of pregnant WLHIV in Africa, those with severe anemia (Hgb < 8.5 g/dL) had a 2-fold increase in preterm births compared to women without anemia, but no increase was observed in those with moderate anemia (Hgb, 8.5–10.0 g/dL). We observed that WLHIV with severe anemia (Hgb < 10 g/dL) and those with moderate anemia (Hgb, 10–10.9 g/dL) had similar risks for preterm birth. General mechanisms could include hypoxia, leading to maternal/fetal stress and spontaneous preterm labor, or oxidative stress (38). Among pregnant women living with HIV in low- and middle- income countries, the prevalence of anemia is higher (73–82%) than what we observed (39, 40). In 1 study, the risk of a preterm birth was 2 times higher in women with severe anemia (40).

It is likely that many women in our cohort were anemic at conception or had low iron stores without frank anemia, based on a large study of non-pregnant WLHIV in the United States, where 36.7% were anemic at study entry (30). Women require at least 300 mg of stored iron just before conception to meet iron demands in pregnancy (41). Even in high-income countries such as the United States, over 50% of women 15–45 years of age have iron stores < 300 mg. While low iron intake was more prevalent in women with anemia in our pregnant WLHIV, the majority of women had adequate intake.

We recognize several limitations to our study. We relied on available Hgb values from routine medical care. We do not know the women's anemia status at conception or in the first/second trimester, or when they began taking supplements. Ferritin, an acute phase reactant, may not adequately reflect iron stores in WLHIV with underlying inflammation. Other markers, such as the soluble transferrin receptor concentration (37) or Reticulocyte

Hemoglobin Content, are less affected by inflammation and may be informative in this context, but such data were not available in this study. Additionally, we do not have information on prior preterm birth history, which is the most significant risk factor for preterm birth, nor on the etiologies of preterm birth in this cohort; future work on these issues should address these limitations. We did not have information on other chronic inflammatory conditions or cancers. Thus, if these cases existed we were not able to exclude them. Finally, we could not characterize other types of anemia outside of IDA, because we did not have access to comprehensive clinical diagnostic testing.

The elevated prevalence of preterm birth associated with anemia in our cohort highlights the importance of screening and treatment of anemia and/or iron deficiency in pregnant WLHIV. Nutritional counseling in WLHIV of childbearing age may be a pathway through which preterm births may be mitigated in this highly susceptible population. Expanded treatment of iron deficiency, such as intravenous iron therapy, in pregnant WLHIV may be an important public health measure (42, 43). In addition, more research is necessary to understand the underlying factors related to the higher prevalence of anemia in black and non-Hispanic WLHIV in order to optimize maternal health during pregnancy in this population.

We remember Tracie Miller for her early insight about the importance of maternal nutrition in women living with HIV and its potential effect on childhood outcomes. She provided valuable mentorship, guidance, and friendship to all of us.

The following institutions, clinical site investigators, and staff participated in conducting PHACS Surveillance Monitoring for ART Toxicities Study (SMARTT) in 2018, with institutions in alphabetical order: Ann & Robert H Lurie Children's Hospital of Chicago: Ellen Chadwick, Margaret Ann Sanders, Kathleen Malee, and Scott Hunter; Baylor College of Medicine: William Shearer, Mary Paul, Chivon McMullen-Jackson, Ruth Eser-Jose, and Lynnette Harris; Bronx Lebanon Hospital Center: Murli Purswani, Mahoobullah Mirza Baig, and Alma Villegas; Children's Diagnostic & Treatment Center: Lisa Gaye-Robinson, Jawara Dia Cooley, James Blood, and Patricia Garvie; Keck Medicine of the University of Southern California: Toni Frederick, Mariam Davtyan, Jennifer Vinas, and Guadalupe Morales-Avendano; New York University School of Medicine: William Borkowsky, Sandra Deygoo, and Jennifer Lewis; Rutgers–New Jersey Medical School: Arry Dieudonne, Linda Bettica, Juliette Johnson, and Karen Surowiec; St. Jude Children's Research Hospital: Katherine Knapp, Kim Allison, Megan Wilkins, and Jamie Russell-Bell; San Juan Hospital/Department of Pediatrics: Nicolas Rosario, Lourdes Angeli-Nieves, and Vivian Olivera; State University of New York Downstate Medical Center: Stephan Kohlhoff, Ava Dennie, and Jean Kaye; Tulane University School of Medicine: Russell Van Dyke, Karen Craig, and Patricia Sirois; University of Alabama, Birmingham: Cecelia Hutto, Paige Hickman, and Dan Marullo; University of California, San Diego: Stephen A Spector, Veronica Figueroa, Megan Loughran, and Sharon Nichols; University of Colorado, Denver: Elizabeth McFarland, Emily Barr, Christine Kwon, and Carrie Glenny; University of Florida, Center for HIV/AIDS Research, Education, and Service: Mobeen Rathore, Kristi Stowers, Saniyyah Mahmoudi, Nizar Maraqa, and Rosita Almira; University of Illinois, Chicago: Karen Hayani, Lourdes Richardson, Renee Smith, and Alina Miller; University of Miami: Gwendolyn Scott, Maria Mogollon, Gabriel Fernandez, and Anai Cuadra; and University of Puerto Rico School of Medicine, Medical Science Campus: Zoe M Rodriguez, Lizmarie Torres, and Nydia Scalley.

The authors' responsibilities were as follows – DLJ, AG, LY, KH, RZ, JJ: designed the research; DN, AJM: conducted the research; SS, LH: provided essential reagents or provided essential materials; DLJ: analyzed the data or performed the statistical analysis and had primary responsibility for the final content; DLJ, DN, AG, LY, JJ: wrote the paper; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, the questionnaires, and programs used in the analysis will be made available upon request to and approval by the Pediatric HIV/AIDS Cohort Network.

References

1. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: Systematic review and meta-analysis. BMJ 2013;346:f3443.
2. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, Pena-Rosas JP, Bhutta ZA, Ezzati M. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: A systematic analysis of population-representative data. Lancet Glob Health 2013;1(1):e16–25.
3. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. Public Health Nutr 2009;12(4):444–54.
4. United Nations Standing Committee on Nutrition. Progress in nutrition: Sixth report on the world nutrition situation. Geneva, Switzerland: United Nations; 2010.
5. Le CH. The prevalence of anemia and moderate-severe anemia in the US population (NHANES 2003–2012). PLOS One 2016;11(11):e0166635.
6. WHO. Global nutrition targets 2025: Anaemia policy brief (WHO/NMH/NHD/14.4). Geneva, Switzerland: World Health Organization; 2014.
7. Mildvan D, Creagh T, Leitz G. Prevalence of anemia and correlation with biomarkers and specific antiretroviral regimens in 9690 human-immunodeficiency-virus-infected patients: Findings of the Anemia Prevalence Study. Curr Med Res Opin 2007;23(2):343–55.
8. Levine AM, Berhane K, Masri-Lavine L, Sanchez M, Young M, Augenbraun M, Cohen M, Anastos K, Newman M, Gange SJ, et al. Prevalence and correlates of anemia in a large cohort of HIV-infected women: Women's Interagency HIV Study. J Acquir Immune Defic Syndr 2001;26(1):28–35.
9. Gupta A, Nadkarni G, Yang WT, Chandrasekhar A, Gupte N, Bisson GP, Hosseinipour M, Gummadi N. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): A systematic review and meta-analysis. PLOS One 2011;6(12):e28691.
10. Williams PL, Seage GR 3rd, Van Dyke RB, Siberry GK, Griner R, Tassiopoulos K, Yildirim C, Read JS, Huo Y, Hazra R, et al. A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers. Am J Epidemiol 2012;175(9):950–61.
11. Tassiopoulos K, Read JS, Brogly S, Rich K, Lester B, Spector SA, Yogev R, Seage GR 3rd. Substance use in HIV-infected women during pregnancy: Self-report versus meconium analysis. AIDS Behav 2010;14(6):1269–78.
12. Della Grotta S, LaGasse LL, Arria AM, Derauf C, Grant P, Smith LM, Shah R, Huestis M, Liu J, Lester BM. Patterns of methamphetamine use during pregnancy: Results from the Infant Development, Environment, and Lifestyle (IDEAL) study. Matern Child Health J 2010;14(4):519–27.
13. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and mineral nutrition information system [WHO/NMH/NHD/MNM/11/1] [Internet]. 2011. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf.
14. Kupka R, Msamanga GI, Mugusi F, Petraro P, Hunter DJ, Fawzi WW. Iron status is an important cause of anemia in HIV-infected Tanzanian women but is not related to accelerated HIV disease progression. J Nutr 2007;137(10):2317–23.
15. Cunningham F, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. Williams obstetrics. 24th edition. New York, NY: McGraw-Hill; 2013.

16. Russell ES, Mohammed T, Smeaton L, Jorowe B, MacLeod IJ, Hoffman RM, Currier JS, Moyo S, Essex M, Lockman S. Immune activation markers in peripartum women in Botswana: Association with feeding strategy and maternal morbidity. PLOS One 2014;9(3):e89928.
17. Gibson RS. Principals of nutritional assessment. New York: Oxford University Press; 2005.
18. Soheilykhah S, Mojibian M, Jannati Moghadam M. Serum ferritin concentration in early pregnancy and risk of subsequent development of gestational diabetes: A prospective study. Int J Reprod Biomed 2017;15(3):155–60.
19. Lao TT, Tam KF, Chan LY. Third trimester iron status and pregnancy outcome in non-anaemic women; Pregnancy unfavourably affected by maternal iron excess. Hum Reprod 2000;15(8):1843–8.
20. Miller TL, Jacobson DL, Somarriba G, Neri D, Kurtz-Vraney J, Graham P, Gillman MW, Landy DC, Siminski S, Butler L, et al. A multicenter study of diet quality on birth weight and gestational age in infants of HIV-infected women. Matern Child Nutr 2017;13(4):12378.
21. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, Paul DR, Sebastian RS, Kuczynski KJ, Ingwersen LA, et al. The US Department of Agriculture automated multiple-pass method reduces bias in the collection of energy intakes. Am J Clin Nutr 2008;88(2):324–32.
22. Institute of Medicine. Dietary reference intakes: The essential guide to nutrient requirements. Washington, DC: The National Academies Press; 2006.
23. Blumberg SJ, Bialostosky K, Hamilton WL, Briefel RR. The effectiveness of a short form of the Household Food Security Scale. Am J Public Health 1999;89(8):1231–4.
24. Watts DH, Williams PL, Kacanek D, Griner R, Rich K, Hazra R, Mofenson LM, Mendez HA. Combination antiretroviral use and preterm birth. J Infect Dis 2013;207(4):612–21.
25. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010;125(2):e214–24.
26. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005;162(3):199–200.
27. Textor J, Hardt J, Knuppel S. DAGitty: A graphical tool for analyzing causal diagrams. Epidemiology 2011;22(5):745.
28. Baroncelli S, Pinnetti C, Genovese O, Tamburrini E, Floridia M. Hematological effects of zidovudine prophylaxis in newborn infants with and without prenatal exposure to zidovudine. J Med Virol 2011;83(3):551–6.
29. Nandlal V, Moodley D, Grobler A, Bagratee J, Maharaj NR, Richardson P. Anaemia in pregnancy is associated with advanced HIV disease. PLOS One 2014;9(9):e106103.
30. Berhane K, Karim R, Cohen MH, Masri-Lavine L, Young M, Anastos K, Augenbraun M, Watts DH, Levine AM. Impact of highly active antiretroviral therapy on anemia and relationship between anemia and survival in a large cohort of HIV-infected women: Women's Interagency HIV Study. J Acquir Immune Defic Syndr 2004;37(2):1245–52.
31. Vishnu P, Aboulafia DM. Haematological manifestations of human immune deficiency virus infection. Br J Haematol 2015;171(5):695–709.
32. Vanasse GJ, Berliner N. Anemia in elderly patients: An emerging problem for the 21st century. Hematology Am Soc Hematol Educ Program 2010;2010:271–5.
33. Auerbach M, Abernathy J, Juul S, Short V, Derman R. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. J Matern Fetal Neonatal Med 2021;34(6):1002–5.
34. Weiss JJ, Sanchez L, Hubbard J, Lo J, Grinspoon SK, Fitch KV. Diet quality is low and differs by sex in people with HIV. J Nutr 2019;149(1):78–87.
35. Kruzich LA, Marquis GS, Carriquiry AL, Wilson CM, Stephensen CB. US youths in the early stages of HIV disease have low intakes of some micronutrients important for optimal immune function. J Am Diet Assoc 2004;104(7):1095–101.
36. Bandera A, De Benedetto I, Bozzi G, Gori A. Altered gut microbiome composition in HIV infection: Causes, effects and potential intervention. Curr Opin HIV AIDS 2018;13(1):73–80.
37. Mei Z, Cogswell ME, Looker AC, Pfeiffer CM, Cusick SE, Lacher DA, Grummer-Strawn LM. Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. Am J Clin Nutr 2011;93(6):1312–20.
38. Allen LH. Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. J Nutr 2001;131(2s-2):581S–589S.
39. Antelman G, Msamanga GI, Spiegelman D, Urassa EJ, Narh R, Hunter DJ, Fawzi WW. Nutritional factors and infectious disease contribute to anemia among pregnant women with human immunodeficiency virus in Tanzania. J Nutr 2000;130(8):1950–7.
40. Mehta S, Manji KP, Young AM, Brown ER, Chasela C, Taha TE, Read JS, Goldenberg RL, Fawzi WW. Nutritional indicators of adverse pregnancy outcomes and mother-to-child transmission of HIV among HIV-infected women. Am J Clin Nutr 2008;87(6):1639–49.
41. Goonewardene M, Shehata M, Hamad A. Anaemia in pregnancy. Best Pract Res Clin Obstet Gynaecol 2012;26(1):3–24.
42. Achebe MM, Gafter-Gvili A. How I treat anemia in pregnancy: Iron, cobalamin, and folate. Blood 2017;129(8):940–9.
43. Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188(6):819–30.